STUDY PROTOCOL

Impact of the COVID-19 pandemic on opioid agonist treatment in Ireland: Protocol for an interrupted time series analysis [version 1; peer review: 1 approved]

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Abstract

While opioid agonist treatment (OAT) is the most effective treatment for opioid dependence, it is heavily dependent on regular face-to-face healthcare delivery placing both clients and treatment providers at risk of COVID-19. Following the emergence of COVID-19, policies were rapidly changed in Ireland, with the introduction of national contingency guidelines by the HSE National Social Inclusion Office, beginning in March 2020 to ensure rapid and uninterrupted access to OAT while balancing efforts to mitigate COVID-19 risk. This study aims to assess the impact of the national contingency guidelines, on the quality of OAT care delivered in Ireland.

An interrupted time series analysis will be conducted using anonymised aggregated level data obtained from the Central Treatment List (CTL), the national register of people receiving OAT, administered by the National Drug Treatment Centre Board on behalf of the HSE. Separate segmented regressions will be conducted to estimate the impact of the national contingency guidelines on the following outcomes: (1) number of patients in treatment; (2) number of patients starting OAT; (3) average waiting time for treatment; (4) number of people on waiting list; (5) number of patients dropping out of treatment. The study period will be divided into pre- (March 2019 to February 2020) and post-intervention (April 2020 to March 2021)
segments. Immediate (change in level) and longer-term impacts (change in slope) of changes to provision of OAT in each of the outcomes will be investigated. Regression coefficients (β) and 95% confidence intervals (CIs) will be reported.

**Keywords**
COVID-19, opioid agonist treatment, interrupted time series, addiction services, drug policy, public health, substance use disorder, harm reduction

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Introduction

Although COVID-19 presents a significant threat to everyone, people with opioid dependence are particularly vulnerable to the disease and its sequelae, as they have a higher burden of co-existing health problems\(^1\), with many living in areas of social deprivation, with poor-quality housing or homelessness\(^2\). Opioid agonist treatment (OAT), using methadone or buprenorphine, is the first line treatment for opioid dependence, as it has been shown to be safe and effective in suppressing illicit opioid use\(^3,4\), improving mental and physical well-being\(^5\), and reducing mortality\(^6\). In fact, a recent systematic review identified that risk of all-cause mortality, overdose, suicide, alcohol-related, cancer and cardiovascular-related mortality, were significantly lower for people with opioid dependence on OAT compared to those not on OAT\(^7\). The authors highlighted the importance of increasing access to OAT and maintaining people on OAT who are in critical need of treatment to reduce their mortality risk\(^8\).

Methadone is the most common form of OAT in Ireland, and is available free of charge to all persons undergoing OAT for opioid dependence\(^9\). In 1998, the Misuse of Drugs Regulations were introduced in Ireland, providing the Methadone Treatment Protocol, a model of care which formed the basis for the clinical governance and quality of delivery of drug treatment in Ireland. This coincided with the establishment of a national treatment register, the Central Treatment List (CTL). The 1998 Regulations were updated in 2017 to provide for OAT using buprenorphine. All patients in receipt of OAT for opioid dependence are registered on the CTL, with each person linked to one specific prescriber and a single dispensing site. OAT is provided in specialist outpatient addiction clinics or primary care. There are an estimated 18,988 people with opioid dependence in Ireland\(^9\), with 10,580 recorded as being in receipt of OAT in 2019.

Acting on the recommendations of the 2010 external review of the Methadone Treatment Protocol\(^9\), detailed clinical guidelines for OAT were developed in 2016, to standardise and improve the quality and safety of OAT care\(^10\). The emergence of COVID-19 presented significant challenges to the provision of OAT services within the existing regulations and clinical guidelines, as OAT is heavily dependent on regular face-to-face health care delivery. At the beginning of the pandemic, there were real concerns that disruption to care, particularly access to OAT and other prescribed medication, would have detrimental consequences for people in treatment. Furthermore, it was anticipated that many people would seek treatment during COVID-19 due to disruptions to the supply of illicit opioids. This led to a rapid and coordinated response, to mitigate the spread of COVID-19, while ensuring continued and safe access to OAT, across multiple sectors of the Irish Health and Social Care system. Multiple bodies serving different but overlapping functions came together to facilitate rapid decision making in a highly regulated environment, resulting in the introduction of a suite of national contingency guidelines by the Health Service Executive (HSE) starting from March 2020. These contingency guidelines supported accelerated access to OAT for people not already in treatment, including increased access to buprenorphine, e-consultations and transferring patients, where possible from supervised consumption to take-home doses, with the possibility of up to 14-days’ supply. They also provided for e-prescriptions, home delivery of prescription medications, including methadone or buprenorphine, and needle exchange for those self-isolating. The contingency guidelines also recommended increased prescribing of naloxone, an opioid reversal agent that may mitigate the risks of fatal overdose from opioids, and advice in relation to the management of alcohol and benzodiazepine dependency. Provisions were also made to support people in residential facilities, including isolation hubs and homeless accommodation\(^11\).

Rapid access to OAT is an important marker of quality of patient care, and COVID-19 has perhaps created an opportunity to increase the number of people entering treatment in Ireland. However, growing evidence suggests that the risk of mortality following dropout from OAT is high\(^6,7,12\); therefore, it is also important to review the level of dropout from OAT, alongside numbers in treatment. The aim of this study is to evaluate the impact of the national contingency guidelines introduced from March 2020 on number of patients on OAT, numbers initiating OAT, numbers on waiting list, waiting times, and patient dropout using an interrupted time series (ITS) design. ITS is a strong quasi-experimental research design to evaluate the impacts of health policy interventions where randomization is not possible\(^13\).

Protocol

Study design and data source

Interrupted time series analyses will be conducted using anonymised aggregated level data obtained from the Central Treatment List (CTL), the national register of people receiving OAT, administered by the National Drug Treatment Centre Board on behalf of the HSE. People are registered on the CTL while waiting for a treatment place, and once in treatment clinicians have a statutory obligation to report treatment initiation details to the CTL. Clients’ treatment status on the CTL remains active for up to four weeks from their first day of non-attendance with their treatment provider. During this time, attempts are made to contact the client to encourage them to return to treatment. If no contact is made, and the client does not attend for treatment for four consecutive weeks, an exit form is completed on the CTL. As a mandatory national register, aggregated numbers from the CTL are nationally representative. The RCSI Research Ethics Committee approved this study (REC202009008). Data will be de-identified, aggregated data, and therefore no consent is required for their use. This work will be conducted following the Strobe Standardised Reporting Guidelines for Cross-Sectional Studies, as this study involves a repeated cross-sectional analysis\(^14\).

Inclusion criteria

We will include data recorded on the CTL between March 2019 and March 2021. This time-period was chosen because it includes the period when the national contingency guidelines were implemented (March 2020), and contains a
sufficient run-in phase before the changes were introduced (March 2019 to February 2020), as well as a 12-month follow-up phase to examine the immediate and short-term effects of the contingency guidelines.

Outcome measures
1. Number of patients receiving OAT, defined as the total number of patients in treatment on the last day of each month.
2. Number of patients starting OAT, defined as the number of patients who were initiated on OAT each month. This includes patients who were initiated on OAT for the first time ever and those who were re-initiated following a period of >28 days out of treatment.
3. Average waiting time for treatment, defined as the average time in days between registering on the national waiting list and induction on OAT each month.
4. Number of people on national waiting list on the last day of each month.
5. Number of patients dropping out of treatment, defined as >4 weeks out of treatment.

Statistical analysis
The observation period is March 2019 to March 2021, with data points defined by calendar month. As the contingency measures were introduced from March 2020, March 2020 will be removed from the ITS analysis. A graphical exploratory approach will be undertaken to identify potential outliers, underlying trends and patterns, and any lagged effect of the intervention that may need to be accounted for in the models. Given that we are seeking to determine the immediate and short-term impacts of the changes introduced, we have a relatively low number of data points (12 pre- and 12 post-change); therefore, we will use a priori segmented regressions to fit the data11. We will conduct separate segmented regression models (March 2019 – February 2020 compared to April 2020 – March 2021) for each of the five outcomes, examining the change in monthly level and slope, and present regression coefficients (β) and 95% confidence intervals (CIs). Autocorrelation and partial autocorrelation function plots will be visually inspected, and the Durbin Watson statistic will be used to identify the presence of residual autocorrelation. In the presence of autocorrelation in the model residuals, a generalised least-squares transformation (Prais-Winsten) will be applied to the models. A significance level of α=0.05 will be assumed. Sub-group analyses by sex, age, location and OAT drug (methadone or buprenorphine) will be performed where possible. Data analyses will be performed using Stata/SE v16.0.

Dissemination
Study findings will be submitted for publication in a peer-reviewed journal and to relevant national and international conferences. Our study findings will also be disseminated via a research brief or webinar to relevant stakeholders including HSE Social Inclusion Commissioning Team; Department of Health National Oversight Committee for National Drug and Alcohol Strategy; HSE National Quality Improvement Team; Irish College of General Practitioners; Irish Institute of Pharmacy; College of Psychiatrists of Ireland; and the European Monitoring Centre for Drugs and Drug Addiction. We will also collaborate with UISCE, the national advocacy service for people who use drugs (PWUD), to create a special edition of our research findings in their magazine, which is disseminated nationally to all services where PWUD attend. Findings will also be disseminated through the use of social media such as Twitter.

Study status
Anonymised aggregated level data has been obtained from the Central Treatment List (CTL).

Discussion
The rapid and coordinated response to mitigate the spread of COVID-19, while ensuring continued and safe access to OAT in Ireland, highlights many bright spots of excellent practice across multiple sectors of the Irish Health and Social Care system during a time of crisis. The Programme for Government 2020 has stressed the need to retain many of the contingency measures introduced, to ensure shorter waiting times and reduced risk of overdose. However, questions remain: how feasible is it to continue with all the changes which were implemented at this time of crisis; is it appropriate or indeed safe to continue with all changes; are there any unintended consequences? The HSE National Social Inclusion Office, who coordinates addiction services, along with General Practitioners, Community Pharmacists, and other key workers in addiction services, now face the challenge of optimising available resources while ensuring continued and safe access to OAT, as we learn to live with COVID-19. This project will highlight the impact of the changes introduced during the pandemic on key process and client outcomes.

Data availability
No data are associated with this article.

References


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This protocol describes the planned analysis of an OAT prescribing and management dataset unique to Ireland to determine the impact of COVID-19 changes to OAT policies for prescribing and access to treatment. The authors describe well the rationale for the study in terms of the benefits of OAT for people who are dependent on opiates.

The analysis plan is based on some assumptions made at the beginning of the pandemic. For example that more people would be seeking treatment. The outcome measures are logical but rather simplistic. Some of the changes to policy and practice are not captured in the analysis plan. For example there was a move to longer dispensing intervals with more people taking doses home rather than have consumption supervised. This practice has inherent risk of increasing overdose which has not been captured in the analysis plan. There was also a move to increase naloxone provision which has not been captured in the analysis plan.

The risk of harm from dropping out of treatment is noted by the team. It therefore seems important to also capture the risks of changes to treatment, particularly the occurrence of overdose. This may not be captured in the CTL system, but if it is I recommend some form of analysis on this to measure what the authors describe in the discussion as 'unintended consequences'. Otherwise how will they know what these are?

The statistical analysis is well described and the test seem appropriate.

Overall I think this project is scientifically sound but fairly simple. It perhaps could go further by including analysis on overdose incidents and drug related deaths in patients and then looking at trends of these in relation to the five stated outcomes.

Is the rationale for, and objectives of, the study clearly described?  
Yes

Is the study design appropriate for the research question?
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Yes

**Are the datasets clearly presented in a useable and accessible format?**
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Substance use, prescribing, management of people who use drugs and delivery of care.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Author Response 21 Sep 2021**

Gráinne Cousins, Royal College of Surgeons in Ireland, Dublin, Ireland

Thank you for your review of our proposed study. We agree with the reviewer that capturing drug-related deaths an important outcome. However, this project is funded under the Research Collaborative in Quality and Patient Safety (RCQPS) funding call in response to COVID-19, with funding for a maximum of 12 months. As mortality data is not recorded in the Central Treatment List (the data source for this project), we do not have access to mortality data. Furthermore, while mortality data is recorded in the National Drug Related Death Index, mortality data (including drug related mortality) is not yet available for the observation period due to delays in inquest files being closed. Future work will need to examine mortality once this data becomes available. However, national and international evidence has identified dropping out of treatment as a high-risk period for mortality, so we feel it is important to capture this information to inform current and future services (i.e. are people who were initiated on treatment during COVID-19 retained in treatment).

**Competing Interests:** None